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Philippe Bernard

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LERNER, DAVID, LITTENBERG,  
KRUMHOLZ & MENTLIK  
600 SOUTH AVENUE WEST  
WESTFIELD, NJ 07090

EXAMINER

BALASUBRAMANIAN, VENKATARAMAN

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/522,497	<b>Applicant(s)</b> BERNARD ET AL.	
	<b>Examiner</b> /Venkataraman Balasubramanian/	<b>Art Unit</b> 1624	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 29 December 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 21-41 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21-41 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>1/29/2008</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

The preliminary amendment, which included cancellation of claims 1-20 and addition of new claims 21-41, filed on 12/29/2006, is made of record. Claims 21-41 are now pending.

#### ***Information Disclosure Statement***

References cited in the Information Disclosure Statement, filed on 1/29/2008, are made of record.

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 21 and its dependent claims 22-28 and 36-41 are indefinite as compound Ia & Ib of claim 21 refers to X and Y groups but there is no proper definition of these groups. Claim 21 merely recites several provisos without defining what are Y and X groups. Although claims 22-23 has X and Y definitions, it is not possible to determine whether the scope of X and Y are within the scope of X and Y of claim 21.

In addition, claim 21 is indefinite as it is not clear how R<sub>x</sub> and R<sub>y</sub> taken together form a linear or branched hydrocarbon chain. See choice (ii) of R<sub>x</sub> and R<sub>y</sub> definition.

2. Claim 23 is indefinite as it recites among various groups, sodium benzoate and ethyl benzoate which are compounds not groups. Note R<sub>3</sub> is a monovalent group.

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3. The compound claim 24-26 and pharmaceutical composition claim 36 are improper dependent claims as they fail to further limit claim 21 on which they are dependent. Note these claims recite "or its prodrugs, its bioprecursors and its pharmaceutically acceptable salt base or acid addition salts...". But claim 21 has no such scope and hence claims 24-26 and 36 are of broader scope than claim 21 and are improper dependent claims.

In addition, it is not clear whether claims 24-26 are compound claims or composition claims with pharmaceutically acceptable base or acid addition salts.

4. Recitation of "prodrug thereof" in claims 24-26 renders these claims and their dependent claims indefinite. Prodrugs in general and as noted in specification, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, the definition of various variable groups include such groups, namely esters, amides, alkoxycarbonyl etc. and therefore it is not clear what is the difference between these variable groups and the prodrug groups. There is clear-cut ambiguity as to what is to be considered as prodrug and what is not. Applicants should note that if the variable groups are prodrug, which are in general inactive but becomes active upon in vivo transformation, then the compound bearing the variable group would be deemed as inactive which is not what the claim recites.

Furthermore, the issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of formula (I), but upon metabolism in the body are converted to active compounds falling within the structural scope of formula (I). The claim

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describes the function intended but provides no specific structural guidance to what constitutes a “prodrug”. Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

5. Independent claims 34 and 35 provide for the use of several compounds recited therein but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. In addition, these claims list several compounds and it is not clear the group of compounds as whole to be used for the intended use.

6. The process claims 31-33 are indefinite for more than one reason. Claim 31 recites dielectrophile without showing what this dielectrophile is. Secondly, the term during step a implies step a is in progress then it is reacted with imidate recited in claim 32. The same applies to step b. Replacement of “during” with “in” is suggested. In addition claim 32 and 33 refers to  $\text{NHR}_x\text{R}_y$  but there is no definition of these groups. There should be a reference back to claim 21 for these definitions. The same applies to the variable group Y.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 24-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrug or its bioprecursor of the claimed compounds. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry - to use the invention. "The factors to be considered in making an enablement rejection have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Finding a prodrug or bioprecursor is an empirical exercise. Note want of clear-cut definition of bioprecursor and its distinction from prodrug, the term bioprecursor is treated as prodrug. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism 'de novo', this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active.

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Thus, determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

The direction concerning the prodrug is found in page 12, line 26. There is no working example of a prodrug of a compound the formula (I). The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. It is well established that "the scope of enablement varies inversely degree of unpredictability of the factors involved", 'and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of

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compounds of formula of claim I as well as the presently unknown list potential prodrug derivatives embraced by the word “prodrug”.

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

MPEP 2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claims 37-41 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating rheumatoid arthritis, does not reasonably provide enablement for treating and preventing any or pathologies, any or all diseases including central and peripheral diseases, cancers, bacterial, fungal and viral infections, inflammatory and autoimmune diseases, cardiovascular diseases, nephrological diseases, diseases related to inhibiting a phosphodiesterase type 2 or 4, prion diseases and neurodegenerative diseases etc generically embraced in the claim language. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims.

Instant method of use claims are drawn to 1) A method of treating or preventing pathologies involving neuronal degeneration involving neuronal degeneration is aging,

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senility, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, Down's syndrome, cerebral strokes, peripheral neuropathies, retinopathies (in particular pigmentary retinitis), prion diseases (in particular spongiform encephalopathies of the Creutzfeldt-Jakob disease type), traumas (accidents to the vertebral column, compression of the optic nerve subsequent to a glaucoma, etc.), or a neuronal disorder caused by the action of chemical products and nerve lesions, 2) A method for treating or preventing central or peripheral diseases in a mammal, 3) A medicinal product for inhibiting a phosphodiesterase type 2 or 4, 4) A method of treating a mammal comprising: administration of the medicinal product of claim 39 to said mammal, wherein said medicinal product is an antimicrobial, antiviral or anticancer medicinal product, or a medicinal product having cardiovascular effects, 5) A method of treating or preventing central or peripheral diseases in a mammal wherein said central or peripheral disease is an inflammatory disease, chronic obstructive bronchopathies, rhinitis, dementia, acute respiratory distress syndrome, allergies, dermatitis, psoriasis, rheumatoid arthritis, infections, viral infections, autoimmune diseases, multiple sclerosis, in particular multiple sclerosis, dyskinesias, glomerulonephritis, osteoarthritis, cancer, septic shock, AIDS, Crohn's disease, osteoporosis, rheumatoid arthritis, obesity, depression, anxiety, schizophrenia, bipolar disorder, attention deficits, fibromyalgia, Parkinson's disease and Alzheimer's disease, diabetes, amyotrophic sclerosis, multiple sclerosis, Lewy body dementias, conditions with spasms such as epilepsy, fibromyalgia, central nervous system pathologies associated with senescence, memory disorders, or psychiatric disorder based on the

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various mode of action of instant compounds, for all which there is no enabling disclosure in the specification.

Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of inhibiting a phosphodiesterase type 2 or 4 in general by the instant compounds, instant claims reach through treating any or pathologies including cancers, bacterial and viral infections, inflammatory and autoimmune diseases, cardiovascular diseases, nephrological diseases , inflammatory diseases, prion diseases and acute neurodegenerative diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of phosphodiesterase type 2 or 4, based on limited assay with limited enzyme, it is claimed that treating and or preventing any or all pathologies including those specifically mentioned above in general. The scope of the claims includes not only any or all pathologies but also those conditions yet to be discovered as mediated by phosphodiesterase type 2 or 4 for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the inhibition of kinase provided in the specification.

As for specific diseases, the scope of claims 37-41 includes treatment of various cancers which would include group consisting of lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region. stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers, which is not adequately enabled solely based on the activity of the compounds provided in the specification.

Similarly, enablement for the scope of "inflammation" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and

many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening

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infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

The same applies to autoimmune diseases. The "autoimmune diseases" are a process that can take place in virtually any part of the body. There is a vast range of forms that it can take,' causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are hundreds such diseases, which have fundamentally different mechanisms and different underlying causes. Thus, the scope of claims is extremely broad.

Again, it appears that, because the instant compounds inhibit a phosphodiesterase type 2 or 4, it is recited that, based on the inhibition, any or all infections can be treated with the instant compounds for which there is no adequate written description and enabling disclosure. Infections in general can be by microorganisms and list of pathogenic microorganism is so large that a single class compound would not be effective for treating all infections. For example for bacteria, the list include gram-positive bacteria, including cocci such as Staphylococcus species and Staphylococcus species, acid-fast bacterium, including Mycobacterium species, bacilli, including Bacillus species, Corynebacterium species and Clostridium species, filamentous bacteria, including

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Actinomyces species and Streptomyces species', gram-negative bacteria, including cocci such as Neisseria species and Acinetobacter species, bacilli, such as Pseudomonas species, Brucella species, Agrobacterium species, Bordetella species, Escherichia species, Shigella species, Yersinia species, Salmonella species, Klebsiella species, Enterobacter species, Haemophilus species, Pasteurella species, and Streptobacillus species, spirochetal species, Campylobacter species, Vibrio species, and intracellular bacteria including Rickettsiae species and Chlamydia species. Specific bacterial species that are targets for the antibiotics of the invention include Staphylococcus aureus Staphylococcus epidermidis, Staphylococcus saprophyticus, Streptococcus pyogenes; Streptococcus agalactiae, Streptococcus pneumoniae, Enterococcus faecalis, Enterococcus faecium Bacillus anthracis, Mycobacterium avium, Mycobacterium tuberculosis, Acinetobacter baumannii; Corynebacterium diphtheriae, Clostridium perfringens, Clostridium botulinum, Clostridium tetani, Neisseria gonorrhoeae, Neisseria meningitidis, Pseudomonas aeruginosa, Legionella pneumophila, Escherichia coli, Yersinia pestis, Haemophilus influenzae, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Vibrio cholerae, Vibrio parahaemolyticus, Treponema pallidum, Actinomyces israeli, Rickettsia prowazekii, Rickettsia rickettsii, Chlamydia trachomatis, Chlamydia psittaci, Brucella abortus, Agrobacterium tumefaciens; and Francisella tularensis, for which there is no adequate written description and enabling disclosure.

The same is true for viral infection. For example the list of various viral diseases due to DNA virus such as hepatitis B virus, herpes viruses (e.g., Herpes Simplex Virus,

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Cytomegalovirus (CMV), Epstein-Barr Virus, (EBV)), smallpox virus, or human papilloma virus (e.g., HPV), many human and animal pathogens: flaviviruses, such as dengue fever, West Nile, and yellow fever; pestiviruses, such as bovine viral diarrhea (BVD), and hepaciviruses, such as hepatitis C; filoviruses such as ebola; parainfluenza viruses, including respiratory syncytial; rubulaviruses, such as mumps; morbillivirus, such as measles, picomaviruses, including the echoviruses; the coxsackieviruses; the polioviruses; the togaviruses, including encephalitis; coronaviruses, including Severe Acute Respiratory Syndrome (SARS); rubella; bunyaviruses; reoviruses, including rotaviruses; rhabdoviruses; arenaviruses, such as lymphocytic choriomeningitis, as well as other RNA viruses of man and animal.

The same applies to cardiovascular diseases, nephrological diseases, prion diseases and neurodegenerative diseases.

Applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as autoimmune diseases such as lupus, AIDS psoriasis, lung cancer, brain cancer, pancreatic cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many agents whose mode of action is said to alleviate inflammation.

The scope of the claims involves millions of compounds of claim 1 as well as the thousands of diseases embraced by the terms cancer, bacterial and viral infection, autoimmune disease and inflammatory disease, cardiovascular diseases, nephrological diseases, prion diseases and neurodegenerative diseases.

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Specific diseases group include: group consisting of inflammatory disease, rheumatoid arthritis, inflammatory bowel disease, asthma, dermatosis, psoriasis, atopic dermatitis, autoimmune diseases, tissue and organ rejection, Alzheimer's disease, stroke, epilepsy, Parkinson's disease, atherosclerosis, restenosis, cancer, Hodgkins disease, viral infection, AIDS infection, osteoarthritis, osteoporosis, and Ataxia Telangiectasia. wherein said inflammatory or autoimmune condition is selected from the group consisting of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gout, asthma, bronchitis, allergic rhinitis, chronic obstructive pulmonary disease, cystic fibrosis, inflammatory bowel disease, irritable bowel syndrome, mucous colitis, ulcerative colitis, diarrhetic colitis, Crohn's disease, gastritis, esophagitis, hepatitis, pancreatitis, nephritis, psoriasis, eczema, dermatitis, hives, multiple sclerosis, Lou Gehrig's disease, sepsis, conjunctivitis, acute respiratory distress syndrome, purpura, nasal polyp, lupus erythematosus, conjunctivitis, vernal catarrh, chronic arthrorheumatism, systemic inflammatory response syndrome (SIRS), sepsis, polymyositis, dermatomyositis (DM), Polyarthritis nodosa (PN), mixed connective tissue disease (MCTD), and Sjogren's syndrome, wherein said cardiovascular, metabolic, or ischemic condition is selected from the group consisting of atherosclerosis, restenosis following angioplasty, left ventricular hypertrophy, insulin resistance, Type I diabetes, Type II diabetes, hyperglycemia, hyperinsulinemia, dyslipidemia, obesity, polycystic ovarian disease, hypertension, syndrome X, osteoporosis, erectile dysfunction, cachexia, myocardial infarction, ischemic diseases of heart kidney, liver, and brain, organ transplant rejection, graft versus host disease, endotoxin shock, and multiple

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organ failure, wherein the viral infection is caused by a virus selected from the group consisting of human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, human papillomavirus, human T-cell leukemia virus, and Epstein-Barr virus.

As seen, instant compounds can be used for treating any disease which is a remarkable finding for which there is no adequate support in the specification.

The scope of the claims includes not only treatment but also "prevention of a disease" which is not adequately enabled solely based on the activity of the compounds as phosphodiesterase type 2 or 4, inhibitors provided in the specification at pages 1, 3, 68 and 69. "To prevent" actually means to anticipate or counter in advance, to keep from happening etc. (as per Webster's II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended mammal. Moreover many if not most of diseases cited above are very difficult to treat and hardly possible to prevent as claimed herein. In fact patient who underwent transplant have to be constantly treated with immunosuppressive medications. The fact that there are number of such drugs available and that they have not been able to prevent contradicts instant invention. Note substantiation of utility and its scope is required when utility is

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"speculative", "sufficiently unusual" or not provided. See *Ex parte Jovanovics*, 211 USPQ 907, 909; *In re Langer* 183 USPQ 288 . Also note *Hoffman v. Klaus* 9 USPQ 2d 1657 and *Ex parte Powers* 220 USPQ 925 regarding type of testing needed to support in vivo uses.

No compound has ever been found to treat diseases of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of modern medicine. For example, as for cancer, Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. Dyke et al., *Expert Opin. Investig. Drugs*, 11(1), 1-13, 2002, Matsumoto et al., *J. Smooth Muscle Res.*, 39(4), 67-86, 2003, and Lipworth BJ, *Lancet*, Jan 8, 365(9454): 167-175, 2005. See also Mass, R. D., *Int. J. Radiation Oncology Bio. Phys.* Vol. 58(3): 932-940, 2004 and Fabbro et al. *Pharmacology &*

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therapeutics 93, 79-98, 2002. For fungal infection, see for example the two non-patent literature Turner et al., Current Pharmaceutical Design. 2, 209-224, 1996. and Sugar et al., Diagn. Microbiol. Infect. Dis. 21: 129-133, 1995. Both these references suggest the art is still exploratory and that a single agent may not be able function as antifungal agents for all fungal infection, despite the fact that large number of antifungal agents were known. For bacterial infection, see Snyder et al., J. Med. Liban 48(4): 208-214, 2000 (PubMed Abstract provided), wherein with regards to antibacterial therapies, it is stated that " common bacteria whose susceptibility to antimicrobials is no longer predictable". Note also that despite the fact there are several commercial antibacterial agents are available, it is still difficult to treat several pathogens such as those cause leprosy, meningitis, sexually transmitted infections, anthrax etc. Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.". Clearly that is the case here.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

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1) The nature of the invention: Therapeutic use of the compounds in treating and preventing any or all pathologies including cancer, bacterial and viral infections, inflammatory and autoimmune diseases, cardiovascular diseases, nephrological diseases, prion diseases and neurodegenerative diseases that require kinase inhibitory activity.

2) The state of the prior art: Recent publications expressed that the kinase effects are unpredictable and are still exploratory. See Dyke et al., Matsumoto et al., Lipworth, Mass et al., and Fabro, et al., cited above especially the concluding paragraph. See also Turner et al., Sugar et al., and Snyder et al., cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating and or preventing any or all pathologies including cancer, microbial infections, inflammatory and autoimmune diseases, cardiovascular diseases, nephrological diseases, prion diseases and neurodegenerative diseases with the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating and or preventing any or all pathologies including cancer, infections, inflammatory and autoimmune diseases, cardiovascular diseases, nephrological diseases, prion diseases

and chronic and neurodegenerative diseases and the state of the art is that the effects of kinase inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all cancer, bacterial and viral infections, inflammatory and autoimmune diseases, cardiovascular diseases, nephrological diseases, prion diseases and neurodegenerative diseases related to kinase.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating and or preventing the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re

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Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 34 and 35 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical

Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 21-23, 30-32 and 38-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Darrow et al., US 6,372,743 (Darrow hereinafter).

Darrow teaches several pyrazolo[1,5a]1,3,5-triazines which include instant compounds, composition and method of use to treat hypertension, obesity, anxiety and depression. See column 2, formula 1 and note the definition of various variable groups. Especially note with the given definition of these variables, compounds taught by Darrow et al. includes instant compounds. See column 2-12 for various preferred embodiments, column 21-33 for various schemes for making these compounds and column 34-78 for various compounds made. Note intermediates and final products taught by Darrow include instant compounds.

Claims 21-23, 30-32 and 38-41 are rejected under 35 U.S.C. 102(b) as being anticipated by He et al. US 6,191,131 (He hereinafter).

He teaches several azolo triazines, which generically include compound claimed in the instant claims, for treating anxiety and depression. See formula I on col. 8 and note the definition of Ar, Z, R1 and R3. Especially note Ar can be a pyridyl group with alkyl and alkoxy substituents, R3 can be a 2-aminoalkyl group, Z can be a CR group R being an alkyl and R1 also can be an alkyl. Note with these definitions, He teaches compounds which include that is claimed in the instant claims. See col. 8 through 142

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for the details, process of making, and examples of compounds made including Table 1-7. Especially see Table 7, compounds 1513 through 1613 for various Ar=pyridinyl compounds. Particularly note both 4,6 and 2,6 disubstituted pyridyl compounds are taught including 4-methoxy-6-methyl-pyrid-3-yl and 2,6-dimethyl-pyrid-3-yl. See entry 1549 and 1589 respectively. See claims 28-35 for the method of use.

Claims 21-23, 30-32 and 38-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Gilligan et al., US 6,060,478 (Gilligan hereinafter).

Gilligan teaches several pyrazolo{1,5-a}-1,3,5-triazines which include the same core and substituents in 2, 7 and 8 position embraced in the instant claims. See column 8-45 for various preferred embodiments. For the process see column 47-48, SCHEME 1. Note in lines 19-52, Gilligan teaches the process and the experimental conditions which is also claimed in the instant claims. See column 99-108, Table 2 for various compounds made.

Claims 21-23, 30 and 38-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Suzuki et al. US 5,565,460 (Suzuki hereinafter).

Suzuki teaches several pyrazolotriazines for treating Parkinson's disease which include instant compound, composition and method of use. See formula I and note the definition of various variable groups. Note with these definitions, Suzuki teaches compounds which include that is claimed in the instant claims. See entire document. Especially see compound 1 and compound 2.

Claims 21-23 and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Kiyokawa et al. US 5,409,928 (Kiyokawa hereinafter).

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Kiyokawa teaches several pyrazolotriazines for treating prostate carcinoma which include instant compound, process of making and composition. See formula I and note the definition of various variable groups. Note with these definitions, Kiyokawa teaches compounds which include that is claimed in the instant claims. See entire document. Especially see examples 1, 3-23, 29 and 31-33.

Claims 21-23, 30-32 and 38-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Rodney et al. US 5,356,894 (Rodney hereinafter).

Rodney teaches several pyrazolotriazines for treating cardiac and cerebrovascular systems which include instant compound, process of making and composition. See formula I and note the definition of various variable groups. Note with these definitions, Rodney teaches compounds which include that is claimed in the instant claims. See entire document. Especially see examples 119-157.

Claims 21-23, 30-32 and 38-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Caulkert et al. US 5,290,776 (Caulkert hereinafter).

Caulkert teaches several pyrazolotriazines for treating cardiac and cerebrovascular systems which include instant compound, process of making and composition. See formula I and note the definition of various variable groups. Note with these definitions, Caulkert teaches compounds which include that is claimed in the instant claims. See entire document. Especially see examples 1-17.

Claims 21-23 and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Fujii et al. US 4,824,834 (Fujii hereinafter).

Fujii teaches several pyrazolotriazines for treating gout which include instant compound, process of making and composition. See formula I and note the definition of various variable groups. Note with these definitions, Fujii teaches compounds which include that is claimed in the instant claims. See entire document including Schemes 1 through Scheme 7 . Especially see examples 1-187.

Claims 21-23 and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Kruger et al. US 4,892,576 (Kriiger hereinafter).

Kruger teaches several pyrazolotriazines for treating gout which include instant compound, process of making and composition. See formula I and note the definition of various variable groups. Note with these definitions, Kruger teaches compounds which include that is claimed in the instant claims. See entire document including column 3-6 for process of making. Especially see examples 1-77.

Claims 21-23, 30 and 38-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim US 4,734,414.

Kim teaches several pyrazolotriazines for treating gout which include instant compound, process of making and composition. See formula I and note the definition of various variable groups. Note with these definitions, Kim teaches compounds which include that is claimed in the instant claims. See entire document including column 3-6 for process of making. Especially see column 5 for compounds made.

Claims 21-23, 30-32 and 38-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Olson et al., US 6,509,338 (Olson hereafter).

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Olson et al. teaches several pyrazolotriazine compounds for treating anxiety and depression, which include instant compounds. See column 4, formula 1 and note the definition of various variable groups. Especially note when R3 is substituted an alkyl substituted with Ra and Ra is NR6R7, with the given definition of other variables, compounds taught by Olson et al. includes instant compounds. See column 4-8 for various preferred embodiments, column 8-11 for species, and column 17-21 for various compounds made.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

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under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 21-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Darrow et al., US 6,372,743.

Darrow teaches several pyrazolo[1,5a]1,3,5-triazines which include instant compounds, composition and method of use to treat hypertension, obesity, anxiety and depression. See column 2, formula 1 and note the definition of various variable groups. Especially note with the given definition of these variables, compounds taught by Darrow et al. includes instant compounds. See column 2-12 for various preferred embodiments, column 21-33 for various schemes for making these compounds and column 34-78 for various compounds made. Note intermediates and final products taught by Darrow include instant compounds.

Darrow differs from the instant claims in exemplifying only R4 = aryl compounds but not heteroaryl compounds and all other variables generically embraced in compound of formula I.

However, Darrow teaches equivalency of those compounds taught in column 34-78 with those generically recited in column 2-12.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Darrow et al

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and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

Claim 21-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over He et al. US 6,191,131( He hereinafter).

He teaches several azolo triazines, which generically include compound claimed in the instant claims, for treating anxiety and depression. See formula I on col. 8 and note the definition of Ar, Z, R1 and R3. Especially note Ar can be a pyridyl group with alkyl and alkoxy substituents, R3 can be a 2-aminoalkyl group, Z can be a CR group R being an alkyl and R1 also can be an alkyl. Note with these definitions, the He teaches compounds which include that is claimed in the instant claims. See col. 8 through 142 for the details, process of making, and examples of compounds made including Table 1-7. Especially see Table 7, compounds 1513 through 1613 for various Ar=pyridinyl compounds. Particularly note both 4,6 and 2,6 disubstituted pyridyl compounds are taught including 4-methoxy-6-methyl-pyrid-3-yl and 2,6-dimethyl-pyrid-3-yl. See entry 1549 and 1589 respectively. See claims 28-35 for the method of use.

He teaches equivalency of the exemplified compounds with those claimed for compound of formula I in the definition of R1, R2, Z and Ar and examples teaches choice of methoxy and methyl in the pyridyl ring. Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in triazine ring and the pyridyl ring including 2-methoxy and 6-methyl groups as permitted by the reference and expect resulting compounds

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(instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Claims 21-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gilligan et al., 6,060,478.

Gilligan et al. teaches several pyrazolo{1,5-a}-1,3,5-triazines which include the same core and substituents in 2, 7 and 8 position embraced in the instant claims. See column 8-45 for various preferred embodiments. For the process see column 47-48, SCHEME 1. Note in lines 19-52, Gilligan et al., teaches the process and the experimental conditions which is also claimed in the instant claims. See column 99-108, Table 2 for various compounds made.

Gilligan et al. teaches equivalency of the compounds exemplified in Table 2 with those generically recited for formula I.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds taught by Gilligan et al., to make 5-amino substituted compounds and expect resulting compound to have CRF activity taught by the art in view of the equivalency teaching outline above.

Claims 21-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olson et al., US 6,509,338

Olson teaches several pyrazolotriazine compounds for treating anxiety and depression, which include instant compounds. See column 4, formula 1 and note the definition of various variable groups. Especially note when R3 is substituted an alkyl substituted with Ra and Ra is NR6R7, with the given definition of other variables,

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compounds taught by Olson includes instant compounds. See column 4-8 for various preferred embodiments, column 8-11 for species, and column 17-21 for various compounds made.

In addition, Olson teaches equivalency of those compounds taught in column 8-11, 17-21 with those generically recited in column 4-8.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Olson and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

### **Conclusion**

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For

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more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

/Venkataraman Balasubramanian/

Primary Examiner, Art Unit 1624